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Letter to the Editor

Duchenne Muscular Dystrophy and Idiopathic HyperCKemia in a Family Causing Confusion in Genetic Counselling

To the Editor:

We read with interest the report of Frydman et al. [1995] who described a child with DMD whose father had idiopathic hyperCKemia. We have been following another family in which both DMD and presumed idiopathic hyperCKemia are seen, in which for several years there was confusion in the genetic counselling that could be offered.

The propositus (III-3) was referred at 5 years with a history of global delay and falling frequently. The diagnosis of DMD was made on the basis of elevated serum creatine kinase CK (13,000 Iu/l) and characteristic muscle biopsy appearance. There was no family history of muscle disease. The patient's mother had two sisters and two nieces, all of whom presented for genetic counselling. Serial CK estimations were performed in all of the female relatives. The mother (II-2) of the propositus

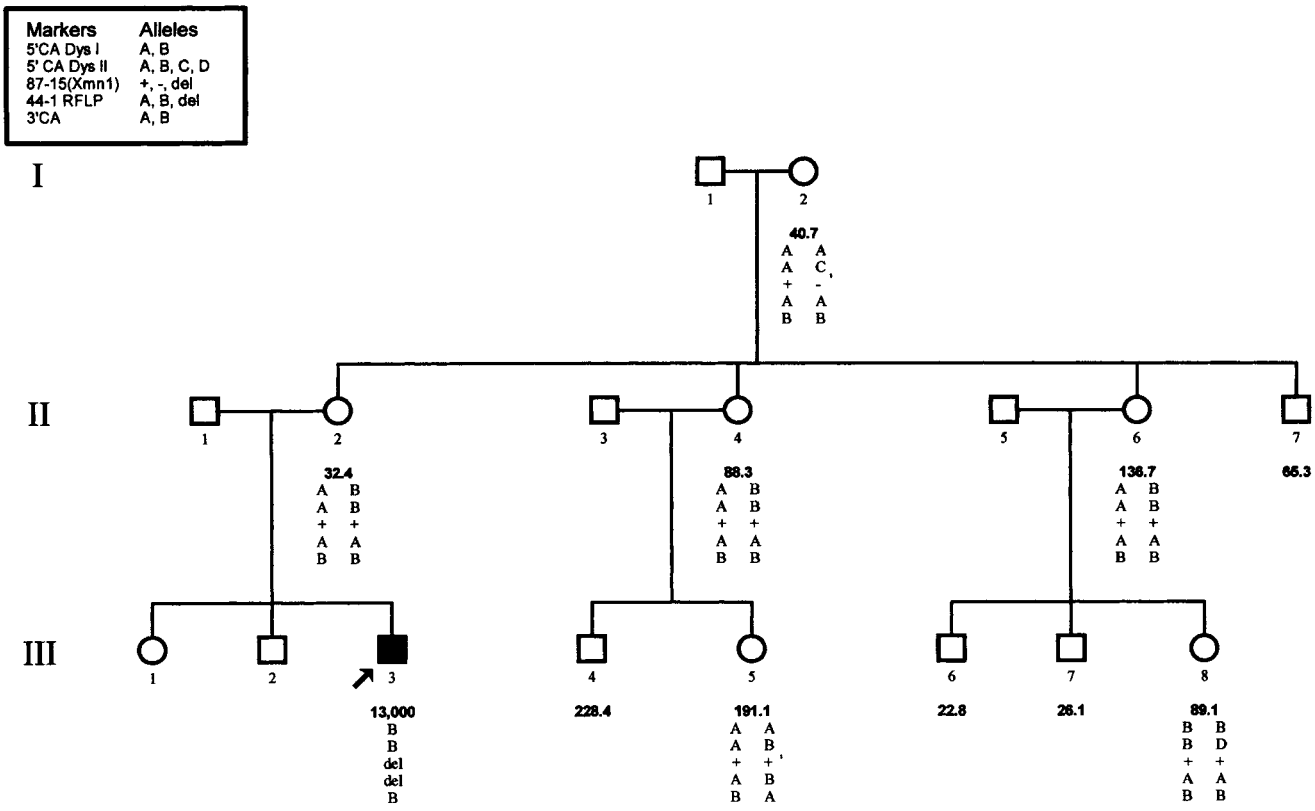

Fig. 1. Pedigree of the family described. The figures in bold represent serum creatine kinase levels (Iu/l N-up to 70) calculated as the mean of at least three samples in the female members of the family. The haplotypes shown span the dystrophin gene.

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had consistently normal CK levels; however, high or borderline high levels were found in II-4, II-6, III-5, and III-8 (normal up to 70 Iu/l (Fig. 1). On the basis of these increased CK levels and in the context of the family history of DMD, these individuals were counselled that they were at high risk of being carriers of DMD.

As DNA testing became available, samples were collected from the family and a deletion was detected in the propositus using cDNA probe 44-1. Two of his female relatives (III-5 and III-8) subsequently underwent prenatal diagnosis looking for this deletion, which was not found in either of the male fetuses tested, allowing the pregnancies to continue. As techniques for DNA testing improved, the full extent of the deletion in III-3 was confirmed to involve exons 14–52. This large deletion encompassed two polymorphic intragenic markers available at that time, which were subsequently tested in the female relatives previously thought to be carriers. Two female relatives at risk (I-2 and III-5) were shown to be heterozygous for one each of these polymorphisms, confirming that, in fact, they were not carriers of the DMD deletion seen in III-3. Subsequent analysis using polymorphisms spanning the dystrophin gene showed that different X-chromosomes were segregating in the individuals with high CK, further suggesting that the high CK in these women was not the result of DMD carrier status.

In light of this information, CK was analysed in the healthy male relatives of the family. The results, as illustrated on the pedigree, show that one man (III-4) also had an elevated CK level. An alternative diagnosis of a dominant trait producing hyperCKemia independent of the DMD in the propositus was considered, and further investigations were carried out on individual II-6. CK remained high, but EMG and muscle biopsy results were normal (including dystrophin immunocytochemistry and immunoblotting), although specific testing for susceptibility to malignant hyperthermia was not performed. On direct questioning the only symptom that could be elicited from the relatives with elevations of CK was an increased tendency to cramps following exertion. None had had any episodes of rhabdomyolysis, nor any problems with anaesthetics.

Thus we report a second family in which both DMD and idiopathic hyperCKemia are seen. In the family reported by Frydman et al. [1995], the hyperCKemia was seen in the patient's father and was thought to coexist with DMD in the propositus, possibly causing his early presentation. In contrast, in our family the presence of the hyperCKemia on the mother's side of the family led to years of confusion in genetic counselling before the finding of the large deletion in the propositus allowed a direct method to assess carrier state in the family.

REFERENCES

Frydman M, Straussberg R, Shomrat R, Goebel H, Legum C, Shiloh Y (1995): Duchenne muscular dystrophy and idiopathic hyperCKemia segregating in a family. Am J Med Genet 58: 209–212.

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